

**REMARKS**

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

The Examiner is thanked for indicating that the rejections under 35 U.S.C. §§ 101 and 112 have been withdrawn, and that the rejection under 35 U.S.C. § 103 has been withdrawn in part.

Claims 1, 3-11, 13, and 14 are pending in this application.

**THE REJECTION UNDER 35 U.S.C. § 103(a) IS OVERCOME**

Claims 1 and 3-11 stand rejected under 35 U.S.C. § 103(a) as being obvious over Nicolaou *et al.* (Agnew. Chem. Int. Ed. 1998, 2014-2045, hereinafter “Nicolaou”) in view of Patani *et al.* (Chem. Rev. 1996, 3147-3176, hereinafter “Patani”). Applicants respectfully traverse. The cited references do not render the pending claims obvious.

The Examiner was not persuaded by Applicants’ previous arguments, and disagreed with Applicants’ assertion that a major change in the biological activity would be expected if the C5 ketone were replaced with an SO group. The Examiner maintains that the change from carbonyl to sulfoxide or sulfone has been increasingly used as non-classical biosisosteres.

In response, Applicants argue that one of ordinary skill in the art would not be motivated to combine or even try to combine Nicolaou and Patani and to replace the CO group at the C5 ketone with an SO group. As support, Applicants submit herein a Declaration under 37 C.F.R. § 1.132 by Dr. Ludger Wessjohann. This Declaration asserts that one skilled in the art would not have found the present invention to be obvious over Nicolaou and Patani in light of the teachings in these cited references. For instance, Patani discusses benzophenone dicarboxylic acids as potential inhibitors of Leukotriene B<sub>4</sub> (LTB<sub>4</sub>). Patani indicates that the portion of benzophenone dicarboxylic acids to which a carbonyl is attached is not critically involved in LTB<sub>4</sub> receptor binding, since replacement of the carbonyl with either a thioether, sulfoxide, or sulfone did not significantly affect binding affinity. See Patani, page 3167, left column. One skilled in the art would thereby conclude from Patani that a replacement in a non-critical part of a molecule, *e.g.*,

replacement of CO group with an SO group, would not result in a significant change in biological activity.

Nicolaou then shows that there was a loss of activity when the C5 ketone was reduced or when the C5 substituent was removed, which demonstrates that the CO group at the C5 position is important to the activity of epothilone derivatives. See Nicolaou, page 2040. Taken Patani and Nicolaou together, the skilled artisan would expect that replacement of the CO group with an SO at the C5 position of an epothilone derivative would either not have an impact or would reduce the biological activity of the derivative; yet, in contrast to this expectation, the present invention having an SO group at the C5 position surprisingly showed an improvement in the activity over compounds carrying a CO group at the C5 position.

The Declaration by Dr. Wessjohann also points out that the R-CO-R molecule lies within the same plane, while the R-SO-R molecule is not in a single plane, as the oxygen is positioned above or below the plane created by the R-S-R group. Hence, one skilled in the art would expect that a derivative having an SO group at the C5 position would demonstrate similar levels of activity as a derivative carrying an OH group at C5, which is a reduction in activity as compared to a derivative carrying a CO group at the C5 position. Again, this expectation would dissuade the skilled artisan from replacing the CO group with an SO group at C5. However, as described previously, replacement of the CO group with an SO group did not reduce activity, but instead surprisingly showed similar and even improved levels of activity.

Thus, given the reduction in activity that would be expected to occur with replacement of the CO moiety with the SO moiety, and in consideration of the teachings in Patani and Nicolaou, one skilled in the art would not be motivated to combine Nicolaou and Patani since it could not be expected that the epothilone derivative having the SO moiety at the C5 position would have a similar or improved activity as the epothilone derivative having the CO moiety at the C5 position.

Applicants additionally draw the Examiner attention to a Declaration by Dr. Wolfgang Richter, which discusses experimental data regarding replacement of the CO moiety at the C5 position with a sulfoxide. The Declaration demonstrates that replacement of the carbonyl function by SO results in epothilones with a better or similar activity range against certain cancer cell lines. Such a result would not have been predicted, as the skilled artisan would expect that the activity levels would be reduced in light of the teachings from the cited references.

For the foregoing reasons, the references cited by the Examiner do not render the claimed subject matter *prima facie* obvious under 35 U.S.C. § 103(a). Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

**III. THE PROVISIONAL DOUBLE PATENTING REJECTION IS OVERCOME**

Claims 1 and 3-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 and 22 of copending Application No. 10/535,474 in view of Patani.

Applicants reiterate that the issue of whether there is indeed double patenting is contingent upon the allowed subject matter in both applications. Applicants thereby request that the double patenting rejection be withdrawn or at least held in abeyance until allowable subject matter in both applications is determined. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to Application No. 10/535,474 will be considered.

**CONCLUSION**

In view of the remarks and amendments herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,  
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